Review Article

DOI: 10.7860/JCDR/2026/82094.23131

Surgery Section

Zollinger-Ellison Syndrome: A Narrative Review of Clinical Presentation, Pathogenesis, Diagnosis and Modern Management Approaches

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ABSTRACT

Zollinger-Ellison Syndrome (ZES) is rare disorder which is caused by gastrin-secreting neuroendocrine tumours known as gastrinomas, primarily located in the duodenum or pancreas. These tumours further result in excessive production of gastric acid, leading to recurrent, treatment-resistant peptic ulcers, chronic diarrhoea, and gastroesophageal reflux. Clinical features presented in patient include abdominal pain, weight loss, anaemia, and prominent gastric folds. Diagnosis of ZES is based upon elevated Fasting Serum Gastrin (FSG) levels, low gastric pH, and confirmatory secretin stimulation tests. Imaging methods such as Ga-68 DOTATATE PET-CT and Endoscopic Ultrasound (EUS) help in localisation of tumour, while Multiple Endocrine Neoplasia type 1 (MEN1)-associated cases require additional endocrine screening. Management in such cases involves high-dose Proton Pump Inhibitors (PPI) for suppression of acid and surgical resection is useful for localised tumours. Advanced and metastatic cases may prove helpful from Somatostatin Analogs (SSA) PPI or Peptide Receptor Radionuclide Therapy (PRRT). Novel agents like sunitinib and everolimus control tumour. Early diagnosis, multidisciplinary treatment can thus improve clinical outcomes and quality of life in patients with ZES. The narrative review is inclusive of clinical presentation, pathogenesis, diagnostic, and contemporary management and emerging approaches of ZES.

Keywords: Gastrinoma, Hypergastrinemia, Neuroendocrine tumour, Proton pump inhibitor, Secretin test

INTRODUCTION

The ZES is a rare disorder which is characterised by gastrin-secreting tumours known as gastrinomas that lead to excessive gastric acid production, resulting in recurrent and severe peptic ulcers, which are often found in atypical locations such as the jejunum [1,2]. Most commonly these tumours are located in the duodenum, pancreas, or peripancreatic lymph nodes, and may be sporadic or associated with MEN1 [3]. Sporadic cases contribute around 70 to 75%, and MEN1-associated cases, contributing around 25 to 30%, where the gastrinomas are usually multicentric and can be accompanied by other endocrine tumours like pituitary adenomas or the hyperplasia of the parathyroid [3,4].

ZES is also known as a gastrinoma syndrome due to ectopic gastrin secretion by non β islet cell tumours [5]. The typical triad of ZES consists of severe and recurring peptic ulcers, hypersecretion of gastric acid (which is often more than 2-3 L per day), and gastrin-secreting tumours [6]. The persistent hypergastrinemia further leads to hypertrophy of gastric mucosa and acid hypersecretion, which results into ulcerations and other gastrointestinal symptoms like abdominal pain, diarrhoea, and reflux [5,7]. ZES is estimated to affect 0.1-3 per million people epidemiologically, with an average age of onset approximated to be 41 years, and slightly male preponderant [8].

ZES was firstly described in 1955 by Zollinger RM and Ellison EH, they detailed patients with severe, recurrent peptic ulcers in the jejunum, which were refractory to conventional treatments, along with massive gastric acid hypersecretion (2-3 L per 12 hours) and associated non β islet cell pancreatic tumours [7,9]. By the 1970s, endocrine surgeons and physiologists delineated the roles of gastrin and non β-islet-cell tumours in provoking gastric acid hypersecretion and ulceration [1,7]. In the late 1980s, the advent of acid-suppressing drugs like H_2-blockers and, later, proton-pump inhibitors revolutionised medical management, which caused reduce in need for gastrectomy [10,11].

Clinical Manifestations of Zollinger-Ellison Syndrome (ZES)

The ZES primarily presents with symptoms which are caused by massive gastric acid secretion driven by gastrin-secreting tumours (gastrinomas) [12]. The primary symptoms of ZES are severe and refractory pain, located in the epigastric or abdominal area, caused by peptic ulcers, which may be multiple, recurrent, and may be located at more distal sites, such as the jejunum, and resistant to therapies [12,13]. Gastroesophageal reflux with heartburn is also common which leads to complications like oesophagitis, strictures, or Barrett's esophagus [14]. In some cases, gastrointestinal bleeding is also an initial clinical presentation, which manifest as haematemesis or melena from ulceration [14,15].

Diarrhoea affects most of the patients which may be the earliest or even sole symptom in very few cases [16]. Diarrhoea results from inactivation of pancreatic enzymes and bile salts due to acid, resulting into malabsorption and secretory diarrhoea, sometimes steatorrhea [17]. Nausea, vomiting, weight loss, anorexia, and anaemia secondary to chronic bleeding are also noted in few patients of ZES [18]. Prominent gastric folds are observed on endoscopy of patient which reflects parietal cell hyperplasia due to sustained stimulation of gastrin [17,18]. Thus, the clinical scenario of ZES is marked by symptoms of refractory peptic ulcer, chronic diarrhoea, acid reflux, and their systemic associated consequences [15].

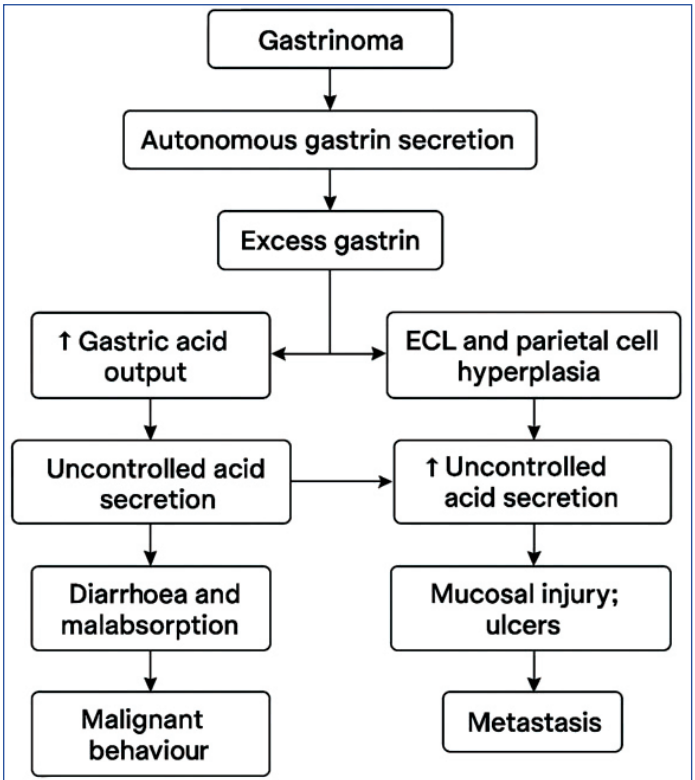
The ZES tends to manifest itself at an earlier age in MEN1 patients and can be diagnosed in earlier age than in isolated occurrences [19]. Multifocal gastrinomas (usually in the duodenum) are common in MEN1-associated ZES, and can be metastatic even though they are smaller than the sporadic ones [3,19]. The prolonged exposure to acid also exposes such patients to severe oesophageal issues, including strictures and Barretts oesophagus [4]. Interestingly, the entire clinical course of MEN1-related ZES has a tendency of being more indolent and having lower disease-associated deaths

and the option of delaying surgery without considerably influencing their survival [4]. Thus, the clinical scenario of ZES is marked by symptoms of refractory peptic ulcer, chronic diarrhoea, acid reflux, and their systemic associated consequences, which can be modified in onset, severity, and tumour characteristics by the presence of MEN1 [19].

Pathogenesis of Zollinger-Ellison Syndrome (ZES)

The ZES is caused by gastrinomas, which are neuroendocrine tumours located in the gastrinoma triangle of the duodenum or pancreas, which secrete gastrin autonomously, thus bypass normal regulatory loops [20]. In physiologically healthy person, gastrin released by G-cells stimulates Enterochromaffin-Like (ECL) cells via CCK-B receptors to release histamine, which then activates parietal cells to secrete acid [20,21]. This balance is disrupted by gastrinomas due to production of excess gastrin, driving both direct and histamine-mediated hypersecretion of hydrochloric acid, and also inducing ECL and parietal cell hyperplasia [19,22]. The result is profound gastric acid output often five times above normal levels which overwhelms defensive mechanisms in the stomach and duodenum [22].

This uncontrolled acid secretion causes extensive mucosal injury along with multiple, refractory, and distal ulcers in duodenum, jejunum, which are resistant to standard ulcer treatments [23]. The state of hyperacidity causes imbalance in absorption of nutrients (fats, leading to steatorrhoea) along with disruption of gastrointestinal motility, resulting in diarrhoea and malabsorption symptoms [24,25]. Moreover, these gastrinomas frequently exhibit malignant behaviour, of which metastasis to lymph nodes or liver is common, an aspect which contributes to the progressive and complex nature of ZES [26]. Pathogenesis of ZES is shown in flowchart [Table/Fig-1].



[Table/Fig-1]: Pathogenesis of Zollinger-Ellison Syndrome (ZES) [19-26].

Diagnostic Approach to Zollinger-Ellison Syndrome (ZES)

The diagnosis of ZES depends upon a combination of clinical features, biochemical tests, and imaging [27]. Patients typically present with recurrent, severe, and treatment-resistant peptic ulcer, which is beyond duodenal bulb, also presents with symptoms of abdominal pain and chronic diarrhoea [27]. The diagnosis focuses mainly on increased FSG levels which are typically >1000 pg/mL, along with presence of a low gastric pH (<2), which strongly suggests a gastrin-secreting tumour (gastrinoma) [28,29]. Secretin stimulation test is specifically helpful in patients with modestly increased FSG levels (200-1000 pg/mL) [30]. In this test an intravenous bolus of secretin is given and the serum gastrin levels are determined at intervals following the administration of the secretin [30]. Gastrin levels 120 pg/mL and above over baseline is highly suggestive of ZES which has great sensitivity and specificity [30]. It is a particularly useful test when the levels of basal gastrin are inconclusive, though it is an invasive and needs close observation to develop adverse reactions [30]. Besides biochemical confirmation, Basal Acid Output (BAO) is a quantitative method of gastric acid hypersecretion [31]. A BAO above 15 mEq/hour helps achieve the diagnosis of ZES, but the high acidic output is not so specific because it can also be found in various other conditions, including atrophic gastritis or the use of chronic PPIs [31].

The EUS is also very effective particularly in the localisation of pancreatic gastrinomas in preoperative setting, with sensitivity of about 84-88% in intrapancreatic lesions and allowing fine-needle aspiration for cytological confirmation but its sensitivity for small duodenal wall tumours is lower [32]. EUS is operator dependent and invasive, requiring sedation [32]. Ga-68 DOTA-peptide PET/CT has largely replaced the conventional ^{111}In-pentetreotide scintigraphy (Octreoscan) due to its greater resolution, high affinity to somatostatin receptor 2, enhanced lesion detection (particularly with small or metastatic deposits), and very few imaging protocols, rendering it the modality of choice [33,34]. This method is very precise, but is also expensive, and will not be available everywhere [34]. High-resolution contrast-enhanced CT and MRI should always stay as adjuncts: CT is useful in terms of anatomical mapping, in vascular involvement, and extra-pancreatic spread; and MRI is very effective in terms of characterising liver lesions and avoiding the use of ionising radiation in follow-up [35,36].

In cases where non invasive imaging is inconclusive, intraoperative localisation methods like meticulous manual palpation, duodenotomy with submucosal inspection, Intraoperative Ultrasound (IOUS) and endoscopic transillumination significantly increase the overall rate of detection of occult gastrinoma [37]. Intraoperative radioguided surgery with radiolabeled SSA or serial intraoperative gastrin levels can further be used to confirm the total tumour removal [38]. A multimodal test that incorporates biochemical, Ga-68 PET/CT and EUS as well as FNA and intraoperative exploration produces the greatest sensitivity of localising the tumour and curing resection [34,37].

The hypersecretory state and gastrin dependence are determined by the secretin stimulation test and BAO measurement, whereas the localisation of the tumour can be done using the somatostatin receptor imaging and EUS that will play a key role in determining surgical management [30,31,34]. The clinical presentation, biochemical profile, and availability of resources of the patient should be tailored into developing a diagnostic approach that will allow identifying ZES in time and making appropriate therapeutic choices [32]. Careful consideration and exclusion of differential diagnoses like atrophic gastritis, retained antrum syndrome, chronic PPI use, *Helicobacter pylori*-associated gastritis, gastric outlet obstruction, systemic mastocytosis, and idiopathic gastric acid hypersecretion, are required since they can also result in increased serum gastrin levels [27,31,36,39]. Differential diagnosis of elevated serum gastrin levels in suspected ZES is depicted in [Table/Fig-2]. Screening is done for hyperparathyroidism and pituitary tumours is highly recommended in familial cases due to association of ZES with MEN1 [40]. Diagnosis of ZES is detailed in [Table/Fig-3].

Treatment and Novel Strategies for Zollinger-Ellison Syndrome (ZES)

Management of ZES is primarily centred on management of gastric acid hypersecretion and gastrinoma. PPIs such as omeprazole,

Condition	Pathophysiology	Gastric pH	Key differentiating features	References
Zollinger-Ellison Syndrome (ZES)	Gastrin-secreting tumour (gastrinoma) causing marked hyperacidity	<2	FSG >1000 pg/mL, positive secretin test, high BAO (>15 mEq/hr), SSTR imaging localisation	[27,39]
Chronic PPI use	Inhibition of acid secretion → compensatory G-cell hyperplasia → hypergastrinemia	>4	History of prolonged PPI therapy, elevated gastrin with normal/low acid output	[36,39]
Atrophic Gastritis / Autoimmune Gastritis	Loss of parietal cells → reduced acid output → feedback gastrin rise	>4	High gastrin but achlorhydria; positive parietal cell antibodies; ↑ B12 deficiency risk	[31,39]
Helicobacter pylori gastritis	Chronic inflammation alters gastrin regulation	Variable	*H. pylori* testing positive; gastrin elevation modest and reversible after eradication	[39]
Retained antrum syndrome	Residual antrum post gastrectomy continues gastrin secretion into duodenum	Low	History of gastric surgery; hypergastrinemia with high acid output	[39]
Gastric outlet obstruction	Prolonged antral distension increases gastrin release	Variable	Vomiting, distension, obstructive findings on imaging or endoscopy	[27,39]
Systemic mastocytosis	Histamine release stimulates parietal cells → ↑ acid → ↑ gastrin (feedback)	<2	Elevated serum tryptase; mast cell infiltration; flushing, urticaria pigmented lesions	[27,39]
Idiopathic gastric acid hypersecretion	Unknown mechanism leading to excessive acid production	<2	ZES-like symptoms but absence of tumour; negative secretin test	[27,39]

[Table/Fig-2]: Differential diagnosis of elevated serum gastrin levels in suspected ZES.
ZES: Zollinger-Ellison Syndrome

pantoprazole are used in therapy which are highly effective in reducing acid output, promoting ulcer healing, and relieving symptoms [41,42]. High-dose PPIs (e.g., omeprazole 80-100 mg/day or pantoprazole 40-160 mg/day) are tailored accordingly as per individual acid output for symptomatic control in patient, side-effects include vitamin B-12 deficiency and hypomagnesemia with long-term usage [32,41]. Nevertheless, chronic PPI therapy has long-term risks including long-term hypergastrinemia, gastric carcinoid tumours and also safety unknown after 10 years of treatment [41].

In the case of localised gastrinomas, surgical resection is the ideal treatment option, especially when a patient has a sporadic course of the disease because curative resection has a great impact on enhancing survival rates [43]. Surgical intervention is a more complicated option in the case related to MEN1 since the disease is multifocal and more prone to recurrence [44]. Other endocrinopathies related to it, including hyperparathyroidism (potentially exacerbating hypergastrinemia), should also be managed in such patients; therefore, often, parathyroidectomy is done before the operation of gastrinoma [44,45].

Emerging management of ZES include usage of SSAs (e.g., octreotide, lanreotide) which cause inhibition of gastrin release, especially in patients with metastatic, unresectable progression of disease [43]. PRRT shows promise for controlling growth of tumour with agents like ^{177}Lu-DOTATATE and symptoms in

Diagnostic component	Details /Criteria	Clinical significance	References
Clinical suspicion	Recurrent, severe, treatment-resistant peptic ulcers (especially beyond duodenal bulb); abdominal pain, chronic diarrhoea	Initial indicators suggesting hypergastrinemia	[27]
Fasting Serum Gastrin (FSG)	>1000 pg/mL with gastric pH <2	Strongly suggests gastrinoma	[28,29]
Secretin stimulation test	Used when gastrin is 200–1000 pg/mL; a rise ≥120 pg/mL after secretin confirms ZES	High sensitivity and specificity for ZES diagnosis	[30]
Basal Acid Output (BAO)	>15 mEq/hour with gastric pH <2	Supports hyperchlorhydria due to gastrinoma	[31]
Gastric pH measurement	<2	Confirms acid hypersecretion	[28,31]
Rule out differential diagnoses	Atrophic gastritis, retained antrum syndrome, chronic PPI use	These conditions also elevate gastrin levels, so must be excluded	[27,31,36,39]
Tumour localisation imaging	Ga-68 DOTATATE PET-CT, Endoscopic Ultrasound (EUS)	Localises gastrinoma and evaluates for metastasis	[32-34]
MEN1 screening	Screen for hyperparathyroidism and pituitary tumours	Necessary in suspected or familial cases due to ZES–MEN1 association	[40]

[Table/Fig-3]: Diagnosis of Zollinger-Ellison Syndrome (ZES).
ZES: Zollinger–ellison syndrome; FSG: Fasting serum gastrin; BAO: Basal acid output; EUS: Endoscopic ultrasound; Ga-68 DOTATATE PET-CT- Gallium-68 DOTA-peptide positron emission tomography-computed Tomography; MEN1: Multiple endocrine neoplasia type 1; PPI: Proton pump inhibitor

advanced neuroendocrine tumours, including gastrinomas [46,47]. Imaging developments (68Ga-DOTATATE PET/CT) enhance the localisation of tumour and its subsequent staging, which enables better planning of treatment [33,34]. However, the long-term effectiveness and ideal sequencing of these treatments, as well as the combination of them with targeted agents, is yet to be completely understood [33].

Targeted molecular agents have also been studied, specifically, everolimus (an mTOR inhibitor) and sunitinib (a tyrosine kinase inhibitor) that have shown some efficacy in progressive or metastatic gastrinomas, which helped to stabilise the disease and increase the time to progression-free survival [32,48]. Newer targeted and radionuclide therapies including surufatinib and combination therapies (e.g., everolimus+SSA or PRRT+targeted therapy) are undergoing clinical trials and should further improve the outcome of refractory and advanced ZES [49]. Complete surgical resection, absence of hepatic metastases, and low tumour grade are prognostically related with an improved survival [32,44,48]. Follow-up during life is necessary, which includes regular gastrin levels, imaging (CT/MRI or Ga-68 DOTATATE PET/CT) and evaluation of adverse effects of the treatment, to identify recurrence or progression early [34]. Also, the problem of diagnostic limitation, unreliable gastrin tests and the necessity to withdraw PPIs for its measurement can be problematic in monitoring and early identification of recurrence [32,49].

New Insights into Clinical Practice for Zollinger-Ellison Syndrome (ZES)

This narrative review of the literature is a synthesis of the latest developments in the understanding, diagnosis and treatment of ZES, which provides clinicians with the latest evidence-based practice framework [43]. Key novel insights include utility of Ga-68 DOTATATE PET/CT as well as EUS in the accurate localisation of gastrinomas, the role of PRRT and sunitinib analogs in the management of unresectable or metastatic disease, and new targeted therapies that include everolimus with sunitinib as to the progressive tumour [33,47].

Besides, the review also focuses on the subtle clinical course and management differences in sporadic and MEN1-related ZES, with particular attention to personalised clinical treatment [44]. In clinical practice, such knowledge can help physicians to choose a multidisciplinary patient-centered approach: early diagnosis of the disease via biochemical and imaging techniques can be done and help to start acid suppression and immediate surgical intervention, whereas advanced therapies provide patients with complex, metastatic, or recurrent disease with an option [37,43]. Combining these insights can enhance the management of the symptoms, reduce the complication rate, maximise the long-term outcomes, and guide patients of ZES to follow a lifelong surveillance [43].

CONCLUSION(S)

The ZES is rare but clinically significant condition characterised by gastrin-secreting tumours which further cause severe acid hypersecretion, leading to peptic ulcers, diarrhoea, and reflux. Proper diagnosis by using biochemical markers, secretin stimulation test, and advanced imaging is important for effective management. Treatment mainly focuses on suppression of acid using high-dose PPIs and surgical control of gastrinomas, which is done in MEN1-associated cases. Treatment options such as SSA and PRRT are helpful for advanced ZES. Early recognition, individualised management can improve outcomes to further reduce morbidity in affected patients.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jul 18, 2025
- Manual Googling: Dec 23, 2025
- iThenticate Software: Dec 27, 2025 (5%)

ETYMOLOGY: Author Origin

EMENDATIONS: 6

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? NA
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Jul 17, 2025**
Date of Peer Review: **Sep 26, 2025**
Date of Acceptance: **Jan 02, 2026**
Date of Publishing: **Apr 01, 2026**